REMARKS

Entry of the foregoing amendments is respectfully requested.

Summary of Amendments

By the foregoing amendments claims 22, 53-63, 69, 79, 88-91, 97 and 98 are cancelled, claims 47, 78 and 81 are amended and claims 99-116 are added, whereby claims 1-21, 23-52, 64-68, 70-78, 80-87, 92-96 and 99-116 are pending, with claims 1, 23, 39, 72, 78 and 99 being independent claims and claims 64-68, 70 and 71 being withdrawn from consideration.

Support for the new and amended claims can be found throughout the present specification and in the original claims.

Applicants point out that the cancellation of claims 22, 53-63, 69, 79, 88-91, 97 and 98 and the amendments to claims 78 and 81 are without prejudice and disclaimer and Applicants expressly reserve the right to prosecute the cancelled claims and the amended claims in their original, unamended form in one or more continuation and/or divisional applications.

Summary of Office Action

As an initial matter, Applicants note with appreciation that the Examiner has indicated consideration of the Information Disclosure Statements filed August 17, 2004, May 16, 2005, February 7, 2006 and October 27, 2006 by returning signed and initialed copies of the forms PTO-1449 submitted therein.

Applicants note that the Restriction Requirement is made final and claims 22, 53-71 and 88-

91 have been withdrawn from consideration.

The Declaration is objected to because one page thereof allegedly is not legible.

The Specification is objected to because certain trademarks are not recognized therein as such.

Claim 78 is objected to because of an alleged informality.

Claims 1-3, 18-21, 78-80 and 92-96 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA").

Claims 4-7, 12-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, 97 and 98 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of Jaeger, U.S. Patent No. 3,914,425 (hereafter "JAEGER").

Claims 8-11, 37, 45 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and further in view of Findlay et al., U.S. Patent No. 4,650,807 (hereafter "FINDLAY").

All of the elected claims are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable of claims of one or more of co-pending application Nos. 10/736,902, 10/910,806, 10/939,351, 11/012,267, 11/115,293 and 11/115,321.

Response to Office Action

Reconsideration and withdrawal of the rejections of record are respectfully requested in view of the foregoing amendments and the following remarks.

Response to Objection to Declaration

The present executed Declaration is objected to because one page thereof allegedly is not legible.

In response, Applicants herewith submit a Declaration of better print quality. Accordingly, this objection is moot.

Response to Objection to Specification

The present Specification is objected to because certain trademarks are not recognized therein as such. In response, Applicants have amended the specification by capitalizing the trademarks recited therein, thereby rendering this objection moot as well.

Response to Objection to Claim 78

Claim 78 is objected to because of the phrase "wherein the dosage form releases the at least one first morphine derivative at least one of over a different period and at a different rate than the at least one second morphine derivative" recited therein.

In response, Applicants submit that the objected to phrase is a different way of reciting "wherein the dosage form releases the at least one first morphine derivative over a different period and/or at a different rate than the at least one second morphine derivative". Accordingly, the objection to claim 78 is unwarranted and should be withdrawn, which action is respectfully requested.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA

Claims 1-3, 18-21, 78-80 and 92-96 are rejected under 35 U.S.C. § 103(a) as allegedly being

unpatentable over FANARA. The Examiner takes the position, *inter alia*, that the subject matter of present claim 1 would allegedly have been obvious to one of ordinary skill in the art in view of FANARA. In this regard, the rejection mainly relies on col. 2, lines 36-50 of FANARA where it allegedly is taught to simultaneously administer more than one active substance and combining the therapeutic effects of active substances with different pharmacokinetic profiles. The rejection asserts that "[i]n order to have the combine [*sic*] therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities." Page 6, first full paragraph of Office Action.

Applicants respectfully traverse this rejection. In particular, FANARA is primarily concerned with pharmaceutical compositions for the controlled release of active substances (see, e.g., title of FANARA), not with the simultaneous administration of different active substances and for this reason alone, one of ordinary skill in the art has no particular reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states:

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The above passage is to be considered in combination with the passage from col. 5, line 39 to col. 6, line 26 of FANARA (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same unit, this makes it possible to obtain, in a single administration, both the immediate release of a first active substance and the prolonged release of the same or of a second active substance.
>
> Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising
>
> A. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
> B. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.
>
> [...]
>
> Such combined pharmaceutical compositions can be prepared according to various methods known to persons skilled in the art.
>
> More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.
>
> [...]
>
> The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine, hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer).

Nothing in the above passages (or any other passage) of FANARA points in the direction of a dosage form which provides a plasma concentration within a therapeutic range of a first active substance and a plasma concentration within a therapeutic range of a second active substance over similar or substantially coextensive periods of time, respectively. Specifically, FANARA mentions

exclusively immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances (in this regard, see also Table 10 in col. 10 of FANARA which lists the time-dependent release of the drugs in the double-layer tablet of Example 4), but is completely silent with respect to the duration of action of the active substances, let alone the duration of action of one drug in relation to the duration of action of the other drug. Moreover the above underlined passage indicates that the immediate release/controlled release combinations of FANARA are not particularly useful in general but only for cases where "very specific beneficial therapeutic effects" can be obtained by administering two active substances in one dosage form.

It appears that the present rejection relies particularly on the fact that FANARA mentions that "[i]n the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles". However, only with hindsight is it possible to conclude therefrom that the plasma concentrations of the two active substances should be in a therapeutic range over similar or substantially coextensive periods of time. In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

the term "pharmacokinetic profile" is defined as "The characteristics of a drug that determine its absorption, distribution and elimination in the body" (see ANNEX). Accordingly, it is not seen that the fact that FANARA mentions that an immediate release/controlled release combination makes it possible to obtain combined therapeutic effects by means of two active substances having very

different absorption, distribution and elimination in the body renders it obvious to one of ordinary skill in the art to use a corresponding combination in order to provide a dosage form which provides plasma concentrations in a therapeutic range of these two active substances over similar or substantially coextensive periods of time.

Applicants further point out that the Examiner has failed to provide any (written) evidence which shows that differences in release rates of different active substances from a single dosage form result in and/or are conventionally used to provide plasma concentrations in a therapeutic range of two active substances which are present in the single dosage form over similar or substantially coextensive periods of time. In fact, the Examiner has not even cited to a single example of the use of different release rates (and in particular, a combination of immediate release and controlled release) for achieving similar or substantially coextensive periods of therapeutic activity of two different active substances, let alone of two different active substances which comprise at least one morphine derivative with antitussive activity.

Applicants submit that for at least all of the foregoing reasons the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of any of the present claims in view of FANARA. Accordingly, the rejection of claims 1-3, 18-21, 78-80 and 92-96 under 35 U.S.C. § 103(a) over FANARA is without merit and should be withdrawn, which action is respectfully requested.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA in View of JAEGER (and FINDLAY)

Claims 4-7, 12-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, 97 and 98 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and

claims 8-11, 37, 45 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and further in view of FINDLAY. The rejections appear to concede that FANARA alone does not render obvious the subject matter of the rejected claims but alleges that JAEGER or JAEGER and FINDLAY, respectively cure the deficiencies of FANARA in this regard.

These rejections are respectfully traversed as well. Specifically, like FANARA, neither JAEGER nor FINDLAY renders it obvious to one of ordinary skill in the art to provide a dosage form which comprises two different active substances and provides similar or substantially coextensive periods of therapeutic activity of these two different active substances.

Specifically, JAEGER teaches that 6-amino-2-methyl-2-heptanol (heptaminol), a relatively non-toxic compound lacking antitussive effects of its own, can enhance the effect of codeine so that the codeine dosage and the associated side effects may be reduced sharply while achieving a desired antitussive effect (col. 1, lines 11-17). Example 2 of JAEGER describes a three-layer pill wherein each of the layers contains both heptaminol and codeine phosphate. JAEGER also mentions that the compositions described therein may additionally contain antihistamines, expectorants and decongestants. However, it is not seen that this disclosure of JAEGER in combination with that of FANARA renders it obvious to provide the subject matter of any of the rejected claims, and neither has the Examiner provided any explanation in this regard.

Further, FINDLAY appears to have been cited by the Examiner merely in order to show that it is known in the art that (certain) antihistamines may be formulated together with decongestants, antitussives and the like. This is clearly not a reason for one of ordinary skill in the art to provide the subject matter of any of the present independent claims, either.

In view of the foregoing, it is submitted that even in combination with JAEGER and FINDLAY, FANARA is unable to render obvious the subject matter of any of the present claims, wherefore withdrawal of the rejections under 35 U.S.C. § 103(a) over the combined disclosures of FANARA, JAEGER and FINDLAY is warranted as well and respectfully requested.

Response to Provisional Rejection of Claims on the Ground of Non-Statutory Obviousness-Type Double Patenting

All of the elected claims are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable of claims of one or more of co-pending application Nos. 10/736,902, 10/910,806, 10/939,351, 11/012,267, 11/115,293 and 11/115,321.

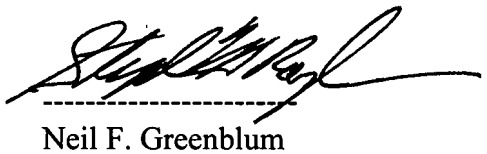
Applicants respectfully request that these rejections be held in abeyance until the Examiner has indicated allowable subject matter. Applicants will then decide if the filing of one or more Terminal Disclaimers is warranted.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

P24615.A06

Respectfully submitted,
Viswanathan SRINIVASAN et al.



Neil F. Greenblum
Reg. No. 28,394

July 6, 2007
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

Stephen M. Roylance
Reg. No. 31,296

ANNEX

Glossary

β-DYSTROGLYCAN The α- and β-dystroglycans are the laminin-binding components of the dystrophin–glycoprotein complex, which provides a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix.

ACETYLCHOLINE A neurotransmitter ($C_7H_{17}NO_3$) that is released at autonomic synapses and neuromuscular junctions. It is active in the transmission of nerve impulses and is formed enzymatically in tissues from choline.

AMINOGLYCOSIDES A group of antibiotics (such as gentamicin) that inhibit bacterial protein synthesis and are particularly active against Gram-negative bacteria.

CYTOTOXICITY The properties of a virus, transgene, vector, compound or molecule that are toxic for cells.

CpG ISLAND Genomic regions that are rich in the CpG pattern, are resistant to methylation and are often associated with promoter activity.

DEPENDOVIRUS A single-stranded DNA virus from the family parvoviridae (subfamily parvovirinae), which is dependent on a co-infection with helper adenoviruses or herpes viruses for efficient replication.

DYSTROBREVINS The components of the dystrophin–glycoprotein complex that bind to syntrophin and (indirectly) to the C-terminal of dystrophin. Dystrobrevin-α recruits signalling proteins, such as neuronal nitric oxide synthase.

ELECTROPORATION The application of an electric current to the plasma membrane of a cell, to temporarily open pores or channels through which DNA might pass.

EPISOMES DNA that can replicate autonomously in the cytoplasm of host cells.

EXTRACELLULAR MATRIX In muscle, this is a thin layer (basal lamina) that contains collagen, elastin and fibronectin, which surrounds each muscle fibre. This might act as a semipermeable filter or a selective cellular barrier and is important in regeneration after damage.

F-ACTIN A protein that is involved in the contractile apparatus and the maintenance of the cytoskeleton of myofibres.

HEK-293 CELLS Host cells that generate viral particles following transfection with the rAAV plasmid and the helper plasmid.

IMMUNOGENICITY The properties of a virus, transgene, vector, compound or molecule that provoke an immune response.

MICROBUBBLES Encapsulated gas microbubbles that can be used as drug or gene carriers, which are able to penetrate into the smallest membranes. When exposed to sufficiently high-amplitude ultrasound, the microbubbles rupture and release the drugs and genes that are contained in their encapsulating layer.

MYOBLAST TRANSPLANTATION The implantation of exogenous muscle-progenitor cells into muscle to generate new myofibres or to support existing myofibres.

NEO-ANTIGEN A foreign (transgene) product that is able to stimulate an immune response.

PHARMACOKINETIC PROFILE The characteristics of a drug that determine its absorption, distribution and elimination in the body.

PRE-mRNA SPLICING The removal of introns from the precursor mRNA molecule; the remaining exons are spliced together.

PRESSURIZED ISOLATED-LIMB PERFUSION The introduction of therapeutic agents under pressure in a limb after isolation of the blood circulation by clamping.

PRIMARY MUSCLE-CELL CULTURES Cells that are taken into culture directly from a tissue biopsy. In contrast to cell lines that only contain immortalized cells, these cultures contain heterogeneous cell populations.

RNaseH Ribonuclease H. An enzyme that cleaves RNA/DNA complexes.

SARCOLEMMA The membrane that encloses a striated muscle fibre.

SPECTRIN A large contractile submembrane protein that, similar to dystrophin, contains an actin-binding domain and a long repeat domain.

SPLICEOSOMAL COMPLEX A large dynamic complex that consists of small nuclear RNA molecules and protein components. It mediates the two catalytic steps of the splicing reaction: the excision of introns from the pre-mRNA and the ligation of the two exon termini.

SYNTROPHINS Peripheral membrane proteins that bind to the C-terminal of dystrophin, which might have a role in the process of synaptogenesis.

TRANSDUCTION The transfer of genetic material into a cell using a viral vector.

TRANSFECTION The transfer of exogenous DNA into a cell.